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Clinical Diagnostic Laboratory Play a Crucial Role in the Management of Thyroid Disorders: A Literature Review

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Abstract: Laboratory measurements of thyroid hormones arises from the fact that the patients origin of diseases in many cases cannot be distinguished based only on clinical examination alone and it can be diagnosed by the laboratory assessment. Although, Serum Thyroid Stimulating Hormone (TSH) is the single unique hormone which is able to predict the thyroid status but the TSH measurement by itself sometimes can be misguiding and prevent the full understanding of thyroid patient. Laboratory evaluation of thyroid hormones, TSH, thyroxine (T4) are the least thyroid hormones although there are many other thyroid related parameters which can be measured, if their evaluation was recommended by the physician. There are many reports in the medical circle on the possible misdiagnosis and eventual mistreatment if the proper clinical cooperation between the physicians and clinical laboratory is either disrupted or mistrusted. The aim of this review is to emphasize the importance of close correlation between physician and clinical laboratory to prevent any possible medical mistake. The application of proper methods and techniques and specific requirement of age and gender reference intervals in the laboratory for the thyroid hormones measurements is strongly recommended to have the full confidence of the physician and to avoid misdiagnosis and eventual mistreatments of patients involved.

Key words: Diagnostic laboratory, physician, laboratory techniques, thyroid stimulating hormone, thyroid hormones

INTRODUCTION

Serum Thyroid Stimulating Hormone (TSH), Tetraiodothyronine or Thyroxine (T4) and Triidothyronine (T3) are the three most important hormones which are routinely measured in clinical laboratory on recommendation of physician for the assessment of thyroid function. Also overt hypothyroidism and hyperthyroidism are the two well distinct thyroid disorders, which can be easily identified by the laboratory measurement of TSH, T4, T3 but the other type of thyroid dysfunction test with normal serum T4, T3 but abnormal TSH are now the pattern of some thyroid diseases which constitute a ratio for thyroid disorders, particularly among women. Serum TSH concentration elevated and suppressed in subclinical hypo and hyperthyroidism respectively, although the subject may not show the clinical manifestation of thyroid disease but based on laboratory measurements the patient is involved in some degree of thyroid dysfunction. Serum T4 and T3 can be measured in term of total or free hormones, the main portion of serum T4 and T3 are transported in blood circulation bound mainly to transporter protein named thyroxin binding protein (TBG) which is synthesized in the liver. Only minute amount of T4 and T3 are in free form and they are defined as free T4 and Free T3.TSH, T4, T3, Free T4, Free T3 all are diagnostically valuable when they are compared with the normal reference range which are set up in each laboratory based on the applied method and technical procedure carried out with specific laboratory kit and reference intervals (Fillee *et al*., 2012; Bartalena *et al*., 1991, 1996; Chaler *et al*., 2012). It is still a controversial topic into the clinical advantage of diagnosing subclinical thyroid abnormalities or if subclinical thyroid disorders have the ability to exert a major side effects on affected person. Although, it may not have a profound adverse effect similar to the overt thyroid diseases but subclinical type of thyroid disorders may put its adverse effect on susceptible individuals and pregnant women on maternal and fetus physiological functions. It seems it is the clinical laboratory which in fact can clarify the status of subclinical thyroid disorders, although these type of thyroid diseases may be lost during patient physical examinations. The outcome of Laboratory assessment of thyroid function clearly reveal the thyroid conditions in health and diseases and play a vital role in thyroid malfunction diagnosis initially and treatment strategy following a comprehensive therapeutic regiments by reversing the abnormal TSH, T4, T3 and other thyroid index including, thyroid autoantibodies to

normal reference range. The aim of this review is to elaborate the vital responsibility of medical diagnostic laboratory in the diagnose and managements of thyroid patients. The importance of physician-laboratory interaction for the optimal therapy is also reviewed.

THYROID HORMONE ASSESSMENTS IN DISEASES

Wide range of diseases are accompanied with thyroid malfunction and laboratory investigation of thyroid assessment require the patients status and any therapeutic regiments which is being used by the patients to avoid the interference which can be seen with any condition which can affect the outcome of clinical laboratory measurements. The laboratory measurements of thyroid hormones are obligatory test in many countries for newborns and in fact it should be done in advance of any pregnancy to rule out any misconception and infertility due to thyroid disorders and also avoid any harm to the fetus on condition of pregnancy, although laboratory thyroid function tests are among the routine test during early stage of pregnancy (Zhu *et al*., 2013; Mansourian, 2010b). As it was stated interventional strategy for subclinical thyroid dysfunction is an argument topic in scenario such as pregnancy and infertility and similar sensitive clinical pictures but subclinical hypothyroidism should be taken seriously in early conception and pregnancy itself. It is reported that in case of prolongation of subclinical thyroid dysfunction it should have been taken into a proper medical consideration (Mansourian, 2010a, b).

The subclinical thyroid disorders particularly subclinical hypothyroidism if remain for considerable of time proved to exert some side effect. The clinical laboratory evaluation of serum TSH and thyroid anti-peroxidase enzyme (Anti TPO), can give a clue if the present subclinical hypothyroidism have a tendency into an overt hypothyroidism. From laboratory point of view the laboratory relation between TSH, T4, T3, gives a nearly clear picture in how thyroid function and diagnostically these three thyroid key hormones and their serum concentration are assisting the medical team in how to manage the thyroid abnormality (Mansourian, 2010e, 2010c).

Serum TSH is the single unique hormone which is able to predict the thyroid status but the TSH measurement by itself sometimes can be misguiding and prevent to understand the clear picture of a suspected thyroid patient and can be a confusing laboratory test. There are many interventional indexes which can disturb the real fact if TSH is measured without any assessments of T4 and T3 for least. There are some other factors such as age, gender, female fertility, pregnancy, thyroid auto-antibodies and any other physiological changes which can be interfere with laboratory results. TSH in fact is not a direct thyroid hormone and it is pituitary hormone with thyroid gland as its sole target tissue. In fact if TSH and T4, T3 are measured, one should remember the limitation on the laboratory set up and determination of serum TSH, T4, T3 and manipulation which can interfere technically in the laboratory particularly for the free T4, FreeT3 and a precise cutoff to compare the laboratory data (Chaler *et al*., 2012; Zhu *et al*., 2013; Mansourian *et al*., 2011a, b; Mansourian and Ahmadi, 2010).

The normal reference range for thyroid hormones and particularly TSH should be re-evaluated if the patient is under therapeutic treatment for hypothyroidism or hyperthyroidism. It seems the drugs leading to substitute or suppress the thyroid hormones can interfere with the reference range of TSH and care should be applied while serum TSH concentration is under investigation. As matter of interest the thyroid reference range of normal for thyroid hormone should take into account of any medication if a diagnosis is going to draw from a laboratory examination. One particular and important difficulty is free T4 determination by the laboratory in some clinical cases such as pregnancy in late stage and severs diseases, therefore serum total T4 is being considered as the key index in thyroid hormone assessment and it may be replaced by free T4 in some clinical manifestation although there some controversial argument about it (Bartalena *et al*., 1996, 1991; Fillee *et al*., 2012). Dietary regiments is another important factor in dealing with thyroid hormones measurement, a diet enriched with iodine excess for example can interfere with a normal thyroid hormone test and the laboratory pattern of results indicate some types of thyroid disorder (Bartalena *et al*., 1996, 1991; Mansourian *et al*., 2010a; Mansourian, 2011d).

INDICATION FOR THYROID HORMONES ASSESSMENTS: TSH FIRST LINE IN LABORATORY THYROID FUNCTION TEST

The thyroid patients clinical presentation of thyrotoxicosis and mexedema are so fluctuated which based on clinical examination alone sometimes can be associated with some difficulty and even misleading in the course of treatment. Laboratory evaluation of thyroid hormones, TSH, T4, T3 therefore are strongly recommended for a proper medical diagnosis and treatments thyroid abnormalities (Mansourian, 2010d).

In routine and professional medical care it is a important decision to check the laboratory estimation of thyroid hormones and it is true when you are dealing with females and specifically those with more than fifty years of age, the subpopulation most commonly facing with either of overt or subclinical thyroid diseases. The TSH in normal reference range mainly is an indication of healthy thyroid but it is mostly recommended to be accompanied with T4, T3 measurement to avoid any wrong doing and missing out a thyroid abnormality (Helfand and Redfern, 1998). Although, some believe that T4, T3 and particularly free T4, only should be checked out if TSH remain either elevated or suppressed (Helfand and Redfern, 1998; Mansourian *et al*., 2010b). There are some limitation to the TSH alone laboratory measurement, Although, there is a argument that if TSH is at normal concentration and no other associated disease of pituitary is detected, the subject is with healthy thyroid and retesting of laboratory measurement is not required as long as the subject is cleared from any clinical symptom related to thyroid abnormality but thyroid function tests are strongly recommended prior to any pregnancy but it is a need in early stage of pregnancy to overcome any difficulty for fetus and pregnant women (Alexander, 2010; Danese *et al*., 1996; Shahmohammdi *et al*., 2008; Fillee *et al*., 2012).

In addition to thyroid assessment of elderly women and particularly of child bearing age prior to the pregnancy, in early stage of pregnancy and for certain during whole period of pregnancy, thyroid disorders of any kind can be accompanied with variety of other diseases including pervious thyroid disorders with or without any operation, thyroid autoantibodies,, diabetes mellitus, chronic renal abnormality, neck and head irradiation, patients under therapeutic regiments, cancers, Cushing syndrome, female reproductive system failure, major Thalassemia, some infection, growth hormones treatments, Biological agents, genetic disorders, Pituitary, cerebral irradiation, head trauma, premature newborns with abnormal birth weight and many other diseases (Jenkins and Weetman, 2002; Wiebolt *et al*., 2011; Kaptein, 1996; Sinard *et al*., 2000; Sklar *et al*., 2000; Colao *et al*., 2000; Niepomniszczse *et al*., 2002; Zervas *et al*., 2002; Janssen *et al*., 2004; Eskes and Wiersinga, 2009; Badros *et al*., 2002; Paulides *et al*., 2007; Coles *et al*., 1999; Poretti *et al*., 2002; Schmiegelow *et al*., 2003; Benvenga *et al*., 2000; Rooman *et al*., 1996; Fisher, 1997; Giustarini *et al*., 2006; Antonelli *et al*., 2006; Goday-Arno *et al*., 2009).

Now-a-days, thyroid hormones assessments are widely performed prior, in the middle and even after pregnancy and newborns are checked for thyroid hormone test to prevent neonates mental and physical damages and where and when these simple laboratory tests are not performed it may be followed with catastrophic adverse effects. The neonatal thyroid disorders and specifically hypothyroidism can be simply prevented if it is diagnosed and its origin might have been cured by a simple strategy of iodine supplementation (Lafranchi, 1999; Delange, 1997; Bhatara *et al*., 2002; Mansourian *et al*., 2007; Mansourian, 2011d).

Laboratory indication of thyroid hormones arises from the fact that the patients origin of diseases cannot be distinguished based on physical examination solely, in the proper manner and duly on time. If the patients are on the verge of abnormality without a comprehensive clinical manifestation it only can be diagnosed by laboratory assessment of thyroid function. The other indication arises from the fact that failure to implement laboratory measurement lead the patient go into a situation of even worsen scenario in the course of disease itself. In spite of what have been mentioned the laboratory measurement of particular testing should give an extra informatory result leading to the patient management and subsequent treatment and in addition there are not any adverse effect in doing the laboratory measurements. At the final stage of any medical diagnosis based on the laboratory measurement, the medical team should be in the position to imply a safe therapeutic regiments, with desired therapeutic effects.

There are extensive studies indicating a major portion of thyroid patients are being lost if they are followed only on medical examination alone and study indicate that less than 50% of thyroid diseases with low T4, T3, are diagnosed on time with the clinical assessment and physical examination alone and if the physician decide to diagnose the overt hypothyroidism on clinical manifestation, there are so many patients that do not manifest the clinical symptom of overt hypothyroidism in early stage of thyroid disease (Eggertsen *et al*., 1988; Petersen *et al*., 1991; Mansourian *et al*., 2008; Mansourian, 2010c).The studies indicated that in primary clinic, the medical team may lost some thyroid patients if they want to relay only on the clinical experiences and further studies in this sensitive area show that up to 90% of thyroid patient with laboratory indication of thyroid laboratory disorders are missed out in primary care clinic (Eggertsen *et al*., 1988; Petersen *et al*., 1991; Monzani *et al*., 1993). Even in a professional medical team studies indicated that a major portion of those patients which were diagnosed as thyroid disorders, the laboratory assessment later on proved to be otherwise (Jarlov *et al*., 1998; Zulewski *et al*., 1997; Monzani *et al*., 2001).

Some other studies even indicated that the clinical manifestation of thyroid disorders such as thyrotoxicosis,,is gradually is reduced with increasing chronically age, weight loss, atrial fibrillation (Zulewski *et al*., 1997; Mansourian, 2012a- c).Therefore, it seems wise to introduce new method of clinical manifestation and borderline both in clinical presentation and laboratory assessments of those subject in older age of over sixty to overcome any wrong doing in the elderly patients. Whenever the serial laboratory assessments of thyroid hormones in comprehensive for the physician, the clinical manifestation and presentation of a patients can be a corner stone for and clinical decision for a particular patients to prevent any harm to the patient involved (Toubert *et al*., 2000; Schectman *et al*., 1991).

Although, the overt thyroid abnormality can be diagnosed by physician based on clinical manifestation if it is already have been continued for a enough time to exert it clinical singe but the subclinical form of thyroid abnormality can only be diagnosed based on thyroid hormone assessment and specifically the TSH measurement. In Such thyroid disorder, serum TSH is elevated and suppressed, T4m, T3, may remain in normal references range for subclinical hypo and hyperthyroidism respectively, recently some are in believe that subclinical form of thyroid diseases should replaced with mild version of thyroid diseases (McDermott and Ridgway, 2001). From laboratory point of view as thyroid disorders getting worse, it seems TSH concentration is altered long before T4, T3 concentration suppressed or elevated in hypo and hyperthyroidism, this laboratory presentation is related to the correlation of pituitary-thyroid axis (Nicoloff and Spencer, 1990; Ercan-Fang *et al*., 2000; Ghori *et al*., 2006).

It seems that TSH remain as the most single thyroid assessment parameter and the likelihood of elevated or suppressed TSH might have been occurred Although, the clinical manifestation of thyroid disorder is not presented. There are various reference range for thyroid hormones according to the laboratory kit provided by manufacturing company but the lower and upper limit of normal for TSH lay between about 0.3 to about 6 mu L^{-1} and some studies indicate as the TSH value approaches the higher limit of normal the hypothyroidism may occur eventually and this incidence is even greater for those subjects which are carrying auto-antibodies against peroxidase enzyme, which is responsible for thyroid hormone biosynthesis in thyroid gland (Hershman *et al*., 1993; Morley, 1981; Vanderpump *et al*., 1995).

Serum TSH concentration seems increase with increasing age particularly among women and some studies report that the tendency in TSH increase rate is about five times in seventy compared to twenties in female population (Canaris *et al*., 2000). As it was mentioned earlier the women are more prone to thyroid disorders than men and this incidence progressed with increasing age in both gender. The association between thyroid auto antibody against peroxidase enzyme and both types of thyroid disorders of hypo and hyperthyroidism are well established, Although, ethnicity play a significant role in this area of thyroid hormones metabolism, studies are also demonstrate that the incidence of hypothyroidism is more than hyperthyroidism in both male and female subpopulation) (Canaris *et al*., 2000; Hollowell *et al*., 2002; Shahmohammdi *et al*., 2008; Ghori *et al*., 2006).

The distribution of thyroid disorders are not homogeneously dispersed all over the world and in fact, this prevalence is not similar even in one country. The ethnicity, dietary iodine is among the intervening parameters. It seems those country and sub-population with enough iodine in daily regiment are less prone to hyperthyroidism and in fact it should be mentioned that iodine intake should be carefully regulated to avoid unwanted hyperthyroid consequences due to excessive iodine intake (Kung and Janus, 1996; Szabolcs *et al*., 1997; Aghini-Lombardi *et al*., 1999; Mansourian, 2011d; Mansourian *et al*., 2007).

LABORATORY ASSESSMENT OF SUBCLINICAL HYPOTHYROIDISM

From clinical laboratory point of view the difference between overt and subclinical hypothyroidism arises from the fact that in overt hypothyroidism TSH, T4, T3, or TSH, T4 and TSH, T3 serum concentration are well defined by elevated TSH and suppressed T4 in most of the time but there are occasion in which, the laboratory picture indicate elevated TSH, suppressed T3 but normal T4. In subclinical hypothyroidism Although, serum TSH concentration is elevated more than upper limit of reference range but T4 and T3 are remain in between normal reference range of normal. Based on laboratory assessment of thyroid hormones it is not wise to label an individual with subclinical hypothyroidism, unless TSH is well over upper limit of normal reference range, free thyroid hormones in between normal reference range, clear picture of any therapeutic regiment and elimination of any suspected thyroid hormonal side effect due to the drug therapy, any abnormality interfering with thyroid hormone metabolism and possible pituitary should be omitted, or finally if the elevated TSH, with normal T4, T3 remain for enough time to label an individual with subclinical hypothyroidism. Although, the clinical

manifestation of hypothyroidism is not presented (Hollowell *et al*., 2002; Wartofsky and Dickey, 2005; Flynn *et al*., 2010; Hamilton *et al*., 2008; Brabant *et al*., 2006; Surks *et al*., 2005; Surks and Boucai, 2010; Cooper, 2004; Lazarus, 2007; Mansourian, 2011a-c).

There are some controversial argument about the need to follow up and detect the subclinical hypothyroidism or if there is a benefit for such investigation in clinical term but it is a general approach to clarify women subclinical hypothyroidism particularly during early stage of pregnancy. The term mild hypothyroidism now recently getting attention instead of subclinical hypothyroidism (Wartofsky and Dickey, 2005).

The division among scientists in this field of is wide as ever, Although, some are in the opinion that both hypothyroidism and hyperthyroidism need attention and they should medically checked out and given final treatments. To overcome the difficulty these later workers are in opinion that the upper limit of TSH normal range should be reduced to avoid false result for the thyroid disorder, which will be followed with an overt hypothyroidism (Wartofsky and Dickey, 2005, Klein and Ojama, 2001; Erickson *et al*., 1994).

In spite of all controversy the treatment and follow up of subclinical cases of thyroid diseases still are remain to be useful, Although, there are a lot of argument in if there is any good in managing subclinical hypothyroidism except in some extra ordinary medical condition such as pregnancy or screening the older women of more than fifty years ago. In routine and professional medical care it is a important decision to check the laboratory estimation of thyroid hormones and it is true when you are dealing with females and specifically those with more than fifty years of age when ever refer for further clinical attention (Surks *et al*., 2004; Surks, 2005). It is a general belief, that laboratory investigation of thyroid hormone should have had indication and also the cost effectiveness of any laboratory test taking into account. In addition to that the ethnicity, other surrounding factors which may interfere with laboratory results should be looked at carefully, if one wants to get a fruitful knowledge, conclusion and subsequent diagnosis and treatment out of the list of laboratory measurements.

LABORATORY ASSESSMENT OF THYROID HORMONES PRIOR, DURING AND AFTER PREGNANCY

Extensive studies in physiology of pregnancy indicate that thyroid hormone play a very crucial role in the pregnancy outcome particularly in the early stage of pregnancy and autoimmunity to the thyroid gland should be also checked out and clarified in the course of pregnancy (Abalovich *et al*., 2007; Burman, 2009; Mansourian, 2010b; Shahmohammdi *et al*., 2008; Mansourian *et al*., 2010a).

Many adverse effect of thyroid disorder on outcome of pregnancy such as abortion and premature infants can be revered following thyroid hormone therapy and this is true even if it is a subclinical type of thyroid disorder, so it is a mater urgency to check every woman prior, during of pregnancy for the sake of fetus and a maternal thyroid hormone which has tremendous effect for growing fetus and pregnant women simultaneously (Negro *et al*., 2006; Vaidya *et al*., 2007; Casey *et al*., 2005; Zhu *et al*., 2013).

The estimation of free T4 is also a matter for discussion, some believe that as pregnancy progressed the freeT4 concentration reduced but one cannot accept this for certain due the laboratory technical limitations and most probable that the pregnancy itself, which is associated with various physiological changes may have side effect to manipulate the accuracy of free T4 testing (Ball *et al*., 1989; Roti *et al*., 1991; Sapin and d'Herbomez, 2003; Lee *et al*., 2009; Wartofsky and Handelsman, 2010; Bartalena *et al*., 1991, 1996).

Some other studies indicated that it seems serum total T4 concentration can be in more benefit for laboratory pregnancy test than freeT4 due to its limitation, which is existed for free T4 explanation result. Even when the effect of elevated estrogen concentration during pregnancy on extra TBG production by the liver taking into account (Lee *et al*., 2009).

It is widely advised that normal reference range of thyroid hormone should have been set up for pregnancy duration and specifically for each trimester of pregnancy. Following this set up thyroid hormones measurement and evaluation can get to a comprehensive conclusion. By then it should be mentioned that serum TSH concentrations is a thyroid hormones index which can be relied on confidently to be one of diagnostic parameters during the pregnancy period. Taking into account the stimulating role of Human Chorionic Gonadotropin (HCG) for the thyroid hormone, one should remember that serum T4 concentration is elevated during pregnancy and in particular at the end of first trimester of pregnancy as the HCG is at its highest peak. Due to similarity of TSH and, TSH receptor on thyroid gland can be stimulated by HCG and studies indicate, the elevated T4 during early stage of pregnancy originated from this fact and such manifestation by HCG, on thyroid gland which is followed by extra concentration of T4, will have an inhibitory effect on the production of TSH from pituitary gland. In addition to what was mentioned the interference due to laboratory

technical methods and procedures specifically for free T4 also should have been taken into consideration particularly during pregnancy. In analyzing the serum thyroid hormones concentration, all of these aspects which may have some role in interpretation of thyroid assessment should be carefully looked at (Roti *et al*., 1991; Sapin and d'Herbomez, 2003; Lee *et al*., 2009; Stricker *et al*., 2007; D'Herbomez *et al*., 2003; Mansourian, 2011b, c).

There are some arguments about the time which female pregnancy thyroid hormones evaluation should be carried out to have an even better comprehensive conclusion out of this thyroid testing for a pregnant women. Doing that earlier testing is to avoid possible catastrophic effect for the pregnant women and the carrying fetus. Laboratory confirmation of thyroid hormone status and particularly in case of hypothyroidism hormone substitution therapy can prevent the adverse of thyroid hormone deficiency which is so strongly is required during early stage of pregnancy for the growing physical and mental growth of fetus. Although, physical growth may be cured for an infant which is born from hypothyroid mother but the mental disorder and the brain retardation due to thyroid hormone deficiency may not be reversed. Therefore here the role of laboratory in having a healthy newborn is well comprehended. It is well advised to have even thyroid hormones laboratory assessment prior the onset of pregnancy especially among women with some other non thyroidal diseases such as insulin depended diabetes and some female reproductive failure, including miscarriage and infertility disorder which can be associated with thyroid abnormalities (Abalovich *et al*., 2007; Fillee *et al*., 2012; Zhu *et al*., 2013).

Additionally it is mentioned that concentrating only and solely on women diagnosed of with high risk factor, defiantly will be accompanied with many pregnant women which looked healthy without any thyroid disorders, on clinical presentation but in fact women with thyroid diseases or on verge of pregnancy are left out. It is now strongly recommended to carry on laboratory hormones assessment in very early on pregnancy to prevent fetus brain damage, which may not be recovered later on, due to the importance of thyroid hormone requirements in very early days of pregnancy (Horacek *et al*., 2010; Burman, 2009; Thung *et al*., 2009; Alexander, 2010).

It seems that the TSH is the single most important laboratory test for the well being of thyroid assessment during pregnancy, Although, thyroxin T4 evaluation is also an crucial test but some in believe that maternal serum TSH concentration can give enough information for the safe pregnancy and thyroid involvement. The other vital thyroid test is the determination of antiperoxidase enzyme and try to treat it in involved pregnant women with normal maternal serum concentration of TSH, T4 level specifically during the first trimester of pregnancy before it is very late for the onset of pregnancy to avoid miscarriages and giving birth to the premature infants. In fact the evaluation of thyroid autoantibodies are so vital to be determined to prevent subsequent thyroid malfunction during and after pregnancy period (Negro *et al*., 2006; Thangaratinam *et al*., 2011; Lazarus, 2011).

Other study indicated that about half those pregnant women being on thyroid hormone replacement therapy of either hyper and hypothyroidism are on an uncorrected thyroid therapy and maternal serum TSH concentration are in suppressed and elevated levels compared to TSH concentration in to reference range of normal. This later scenario, most probably will be accompanied with clinical condition with catastrophic effect on eventuality of pregnancy. On the base of these expecting clinical manifestation thyroid hormone therapy should be routinely checked out by laboratory assessment of thyroid hormone prior to the pregnancy and thyroid hormone therapy should be adjust accordingly to have a safe conception in eventual pregnancy (Hallengren *et al*., 2009; Aexander *et al*., 2004).

One other important issue in the management of thyroid replacement therapy in pregnancy and specifically the assisted pregnancy require an even extra ordinary requirements of substitute thyroxine therapy to prevent the possible sever hypothyroidism in the prior period and during expected pregnancy (Stuckey *et al*., 2010).

During the pregnancy period the level of thyroxine substitute therapy should be adjusted according to the laboratory estimation of serum TSH concentration but as this will be very late to correct the thyroxine replacement it is strongly recommended to have optimum thyroxine replacement at early conception to avoid fetus mental and brain damage due to the lower thyroxine in the initial phases of pregnancy (Abalovich *et al*., 2007; Alexander *et al*., 2004).

Those women treated for hyperthyroidism, of Graves during pregnancy care should be taken into account, by checking the serum laboratory TSH concentration to have the TSH level well controlled to be at least in the lower region of normal reference range to prevent any abnormality in fetus life due to hyperthyroidism as well (Luton *et al*., 2005; Casey *et al*., 2006; Sato *et al*., 1977).

Care should be taken in laboratory assessment of pregnant women thyroid hormones after giving birth to the new infant, studies indicate thyroid abnormalities following postpartum in females and in fact one study

indicate that about 1/10th females present some type of abnormalities of thyroid gland during six month following giving birth to the newborn. Some of the abnormalities of thyroid gland during this six months including rising serum TSH concentration, elevated serum antioeroxidase level and the scenario even getting worse if a pregnant female which was presented with high serum TSH and were left un attendant even during pregnancy, now sustained a very high serum TSH level and hypothyroidism in about three years after the termination of pregnancy (Abalovich *et al*., 2007; Stuckey *et al*., 2001).

It should be noted that if pregnant hypothyroid female remain untreated following giving birth to infant, will have a risk factor for the next pregnancy, therefore the presentation of hypothyroidism during postpartum period should be assessed by laboratory measurement of serum TSH concentration. Studies indicated that the incidence of hyperthyroidism during postpartum remain to be very low and even the TSH level was suppressed following pregnancy, it has been returned to normal concentration in about one and half year of pregnancy termination and the complication cannot be compared with those cases of hyperthyroidism presenting with high concentration of serum TSH, in addition to all that have been mentioned, high risk females thyroid function should be carefully measured by the serial laboratory measurement of thyroid gland. The understanding of pregnant women thyroid function tests will help to have a comprehensive outlook about the newborn thyroid hormone status or if there is a possible congenital hypothyroidism facing the infant, which can easily be managed based on later information (Stuckey *et al*., 2001; Abalovich *et al*., 2007; Lazarus, 2011; Stagnaro-Green *et al*., 2011).

Dietary status is one other important accept in thyroid disorders and particularly hypothyroidism and specifically during the pregnancy period. The physiological condition during pregnancy enhance the urinary iodine excretion through kidney, therefore, pregnancy itself is a condition with iodine loss in pregnant female. On the base such physiological change during pregnancy, an adequate iodine supplementation should be carefully taken into consideration (Mansourian, 2010a, 2011d; Mansourian *et al*., 2007).

LABORATORY LIMITATION IN PREGNANCY THYROID HORMONE ASSESSMENTS

Estrogen, the Female sex hormones production enhanced during pregnancy and have a profound effect on the biosynthesis of Thyroid Binding Globuline (TBG), due the direct effect of estrogen on liver with subsequent over production of TBG. As result of enhanced TBG production, the serum total T4 concentration is increased but with minor fluctuation in the serum free T4 concentration in pregnant women, this interventional procedure should be taken into account when the laboratory measurement of thyroid hormone of pregnant women are reported and a clinical decision is to be drawn out of the laboratory data (Lebeau and Mandel, 2006).

CLINICAL DECISION MAKING BASED ON LABORATORY THYROID HORMONE MEASUREMENT

Various thyroid disorders are presented with different clinical manifestation and even if physician is going to set up a clinical decision based on clinical and physical manifestation, still the physician confidently cannot say at which level of abnormality the patient is and therefore which clinical set up and medication strategy can be drawn out of the clinical manifestation alone without any laboratory assessment of thyroid hormones. The close correlation between the physician and medical diagnostic laboratory, therefore strongly recommended for the proper thyroid patients management. If this cooperation is going to have fruitful results, both physician and laboratory team particularly should do their thyroid hormones measurements properly with appropriate laboratory techniques, up to date procedures and methods (Covinsky *et al*., 2000; Kailajarvi *et al*., 2000; Ismail *et al*., 2002; Kricka, 2000).

The cooperation and understandable dialogs between physician and laboratory is a crucial step forwards if a permanent interrelation are to be kept alive. Laboratory thyroid hormones measurements should have clinical benefits both for the patients and clinical decision making in on hand and the cost effectiveness of such test performance is another concept which the medical team should take into consideration. The important message of cooperation between clinician and laboratory is the satisfying outcome out of the physician and laboratory axis. Two main and vital steps strongly required to have such coordination between these two important elements in medical team. These include laboratory measurements which exhibiting precision and the performed test can be reproduced, in the laboratory, in one hand and the proper diagnosis which is decided by physician on the other hand (Ransohoff and Feinstein, 1978).

Laboratory measurement of thyroid hormones based on immunoassay procedure, which is expensive tests performed in the laboratory and therefore its cost effectiveness should be taken into consideration to prevent wrong doing in the laboratory and avoid the

unwanted repetition of laboratory thyroid hormone measurement of particular case, which financially exert a heavy burden on the medical laboratory (Ismail *et al*., 2002; Kricka, 2000).

The technical difficulty associated with thyroid hormone measurement by immunoassay method and undesired consequences originated from such delegate procedure, particularly for the estimation of free thyroxin all should be carefully taking into consideration. The other problems interfering with a proper thyroid hormone measurement include different therapeutic regiments for the non thyroidal diseases and rising autoantibody against thyroglobulin are the disturbing risk factors for not having a proper thyroid hormones assessment by the medical diagnostic laboratory which can be a confusing factors in patient management by medical team.

In order to avoid such abnormality in the estimation of thyroid hormone laboratory measurement and free thyroxine due to various intervening factors, the serum total thyroxin value may be preferred instead of free thyroxin in patients suffering from critical diseases and also thyroid hormone measurement prior, during and after pregnancy (Lee *et al*., 2009; Van den Berghe *et al*., 1999; Abalovich *et al*., 2007).

SUBCLINICAL THYROID DISORDERS ARE ACCOMPANIED WITH VARIOUS SIDE EFFECTS

Cardiovascular abnormalities and particularly arrhythmia are among major adverse effect of subclinical thyroid problems, Although, there are some disagreement in this area of thyroid studies (Parle *et al*., 2001; Flynn *et al*., 2010; Razvi *et al*., 2010; Mansourian, 2012b, c). The side effects of subclinical hyperthyroidism which identified with suppressed TSH and T4, T3 in normal reference interval are atrial fibrillation, cardiac function abnormalities, osteoporosis and overt hyperthyroidism (Mansourian, 2012b, c; Martin *et al*., 1993; Sawin *et al*., 1994; Biondi *et al*., 1993, 1996; Wesche *et al*., 2001; Bauer *et al*., 2001; Stott *et al*., 1991; Fade *et al*., 1991). The subclinical hypothyroidism which marked with increased TSH and normal T4, T3 in reference intervals exhibit the possibility of atherosclerosis, coronary artery disorders, congestive heart failure, vascular compliance and subsequent overt hypothyroidism, dyslipidemia, depressive abnormalities, blood coagulation abnormality. Some of these abnormalities can be reversed by medications (Nystrom *et al*., 1988; Huber *et al*., 2002; Hak *et al*., 2000; Rodondi *et al*, 2006; Rodondi *et al*., 2005; Volzke *et al*., 2007; Cappola *et al*., 2006; Lekakis *et al*., 1997; Nagasaki *et al*., 2009; Owen *et al*., 2006; Monzani *et al*., 2001; Danese *et al*., 2000; Meier *et al*., 2001; Haggerty *et al*., 1993; Chadarevian *et al*., 2001; Woeber, 2005; Mansourian, 2010a, c).

Some cases of subclinical thyroid disorders progressed into overt thyroid malfunction and it has been shown that, there is a possibility that serum TSH level may return to reference interval subsequently. On base of all these discrepancy it is strongly advised to practice laboratory measurement of TSH before any thyroid therapeutic treatment, in case TSH is returned to reference interval and treatment is not required based on laboratory TSH measurement, unless clinical manifestation dictate otherwise (Fade *et al*., 1991; Meyerovitch *et al*., 2007). It seems overt hyperthyroidism can be a progression of subclinical into overt and the prevalence of spontaneous overt hyperthoidism is very low (Fade *et al*., 1991; Woeber, 2005; Effraimidis *et al*., 2011; Mansourian, 2010c).

Although, the incidence of osteoporosis in overt hyperthyroidism is well documented but it is not absolutely clear whether subclinical hyperthyroidism have a potential role in bone disorders. In spite of what was mentioned studies indicate that suppressed serum TSH in elderly females is specifically associated with bone fracture of hip and vertebral (Bauer *et al*., 2001; Wesche *et al*., 2001; Ross, 1994).

CLINICAL APPLICATION OF HYPOTHYROIDISM

The initial serum TSH is a golden standard for thyroid estimation in prolonged future and tendency of overt hypothyroidism increased within serum TSH level in the upper region of reference interval of about 4 $m\mu\ L^{-1}$. Thyroid microsomal auto antibody is an inducing factor in progression into overt hypothyroidism (Tunbridge *et al*., 1977; Meyerovitch *et al*., 2007; Huber *et al*., 2002).

Mild and subclinical hypothyroidism are associated with hypercholesterolemia and athersclerosis, with eventual myocardial infraction. The incidence of atherosclerosis is even greater when it is followed by the presence autoantibody against peroxidase enzyme in the thyroid (Hak *et al*., 2000; Adrees *et al*., 2009; Huber *et al*., 2002; Mansourian *et al*., 2008; Mansourian, 2010c; Petta *et al*., 2007; Chu *et al*., 2002).

Hypothyroidism is also can be associated with vascular and cardiac abnormalities, impairing diastolic, systolic pathways and studies shown thyroxine replacement therapy which can bring serum level TSH to a acceptable range in the TSH reference interval can significantly improve the patient clinical condition (Mansourian, 2012b, c; Lekakis *et al*., 1997; Nagasaki *et al*., 2009; Monzani *et al*., 2001; Kahaly, 2000).

Laboratory measurement of TSH and cholesterol, triglyceride indicated that there are direct relation between their serum concentrations (Asvold *et al*., 2007; Waterhouse *et al*., 2007; Mansourian *et al*., 2008; Mansourian, 2010a, c).

Overt hypothyroidism itself markedly is correlated with elevated total cholesterol concentration and serum low density lipoprotein return to normal reference intervals in addition the cholesterol serum, triglyceride can also get inside normal range (Thompson *et al*., 1981).

Psychological disorder is the other clinical manifestation correlated with overt hypothyroid diseases, which can be reversed by thyroxine replacement therapy (Jorde *et al*., 2006; Bell *et al*., 2007; Monzani *et al*., 1993; Mebis *et al*., 2006).

BENEFIT OF LABORATORY SERUM THYROID ASSESSMENT

Progressed thyroid diseases can be accompanied with catastrophic clinical manifestation and fatal outcome. Early determination of serum thyroid hormone can be a valuable diagnostic tool in the physician hand to reverse any harm which may be followed if the thyroid diseases remain unattended and untreated. Laboratory measurement of thyroid hormones in the proper time can prevent thyrotoxicosis, myxedema, which can be missed out by physical examination alone and they can be fatal in their nature. The other benefit originated from early diagnosis by thyroid hormone assessment using laboratory method and technique is to prevent the initial thyroid abnormality enter into a steady and progressed thyroid disease, with potential adverse effects in many cases (Weetman, 1997; Mansourian, 2010a, d, c).

One critical issue in laboratory assessment is based on specificity and sensitivity and having a reliable normal reference range for thyroid hormones measurement in the medical diagnostic laboratory to prevent any mistake in the patient management. On base of many studies it is indicted that TSH, total T4 and T3 can be more useful than TSH, free T4, free T3, due the complication in the free hormones interpretation and laboratory measurements particularly during pregnancy and non-thyroidal diseases, Although, there is not a universal agreement in this regards (Wartofsky and Handelsman, 2010; Fillee *et al*., 2012; Bartalena *et al*., 1991, 1996).

KEY POINTS

Although, single laboratory measurement of serum TSH can give a clue but TSH, T4, T3 are the three most important hormones which are routinely are measured in the clinical laboratory on recommendation of physician for the assessment of thyroid function.

Only minute amount of T4 and T3 are in free form and they are defined as free T4 and FreeT3 but TSH, total T4, totals T3, FreeT4 and Free T3 all are diagnostically valuable when they are compared with the normal reference range.

The outcome of laboratory assessment of thyroid function clearly reveals the thyroid conditions in health and diseases and plays a vital role in thyroid malfunction diagnosis. The subclinical thyroid disorders particularly subclinical hypothyroidism if remain for considerable of time proved to exert some side effects.

Subclinical thyroid disorders can only be diagnosed through laboratory measurement of TSH, T4, T3 and can only be diagnosed by laboratory on condition of normal serum T4, T3 and abnormal serum TSH levels.

Cardiovascular abnormalities and particularly arrhythmia are among major adverse effect of sub clinical thyroid disorders, Although, there is some disagreement in this area of thyroid studies.

In routine and professional medical care it is an important decision to check the laboratory estimation of thyroid hormones and it is true when you are dealing with females and specifically those with more than fifty years of age.

It is widely advised that normal reference range of thyroid hormone should have been set up for pregnancy and specifically for each trimester of pregnancy to prevent fetus mental and physical retardation.

It is a general belief, that laboratory investigation of thyroid hormone should have had an indication and also the cost -effectiveness of any laboratory test taking into account.

Various thyroid disorders are presented with different clinical manifestation and even if physician is going to set up a clinical decision based on clinical manifestation alone, still the physician cannot confidently say the level of abnormality.

One critical issue in laboratory assessment is based on specificity and sensitivity and having a reliable normal reference range for thyroid hormones measurement in the medical diagnostic laboratory to prevent any mistake in the patient management.

The technical difficulty associated with thyroid hormone measurement by immunoassay method and undesired consequences originated from such delegate procedure, particularly for the estimation of free thyroxine which all should be carefully taking into consideration when the patients state of health differentially assessed.

Considering the all above consideration and the existing laboratory limitations, the close correlation

between the physician and medical diagnostic laboratory, are therefore strongly recommended for the proper treatment of thyroid patients to prevent any wrong doing in patient managements.

REFERENCES

Abalovich, M., N. Amino, L.A. Barbour, R.H. Cobin and L.J. De Groot *et al*., 2007. Management of thyroid dysfunction during pregnancy and postpartum: An endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab., 92: S1-S47.

Adrees, M., N. Gibney, N. El-Saiety and G. Boran, 2009. Effects of 18 months of L-T4 replacement in women with subclinical hypothyroidism. Clin. Endocrinol., 71: 298-303.

Aghini-Lombardi, F., L. Antonangeli, E. Martino, P. Vitti and D. Maccherini *et al*., 1999. The spectrum of thyroid disorders in an iodine-deficient community: The Pescoporgano survey. J. Clin. Endocrinol. Metab., 84: 561-566.

Alexander, E.K., E. Marqusee, J. Lawrence, P. Jarolim, G.A. Fischer and P.R. Larsen, 2004. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N. Engl. J. Med., 351: 241-249.

Alexander, E.K., 2010. Here's to you, baby! A step forward in support of universal screening of thyroid function during pregnancy. J. Clin. Endocrinol. Metab., 95: 1575-1577.

Antonelli, A., C. Ferri, P. Fallahi, S.M. Ferrari, A. Ghinoi, M. Rotondi and E. Ferrannini, 2006. Thyroid disorders in chronic hepatitis C virus infection. Thyroid, 16: 563-572.

Asvold, B.O., L.J. Vattan, T.I.L. Nilsen and T. Bjoro, 2007. The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT study. Eur. J. Endocrinol., 156: 181-186.

Badros, A.Z., E. Siegel, D. Bodenner, M. Zangari, J. Zeldis, B. Barlogie and G. Tricot, 2002. Hypothyroidism in patients with multiple myeloma following treatment with thalidomide. Am. J. Med., 112: 412-413.

Ball, R., D.B. Freedman, J.C. Holmes, J.E. Midgley and C.P. Sheehan, 1989. Low-normal concentrations of free thyroxin in serum in late pregnancy: Physiological fact, not technical artefact. Clin. Chem., 35: 1891-1896.

Bartalena, L., F. Bogazzi and A. Pinchera, 1991. Thyroid function tests and diagnostic protocols for investigation of thyroid dysfunction. Ann. Ist Super. Sanita, 27: 531-539.

Bartalena, L., F. Bogazzi, S. Brogioni, A. Burelli, G. Scarcello and E. Martino, 1996. Measurement of serum free thyroid hormone concentrations: an essential tool for the diagnosis of thyroid dysfunction. Hormone Res., 45: 142-147.

Bauer, D.C., B. Ettinger, M.C. Nevitt and K.L. Stone, 2001. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. Ann. Internal Med., 134: 561-568.

Bell, R.J., L. Rivera-Woll, S.L. Davison, D.J. Topliss, S. Donath and S.R. Davis, 2007. Well-being, health-related quality of life and cardiovascular disease risk profile in women with subclinical thyroid disease: A community-based study. Clin. Endocrinol., 66: 548-556.

Benvenga, S., A. Campenni, R.M. Ruggieri and F. Trimarchi, 2000. Hypopituitarism secondary to head trauma. J. Clin. Endocrinol. Metab., 85: 1353-1361.

Bhatara, V., R. Sankar, J. Unutzer and J. Peabody, 2002. A review of the case for neonatal thyrotropin screening in developing countries: The example of India. Thyroid, 12: 591-598.

Biondi, B., S. Fazio, C. Carella, G. Amato and A. Cittadini *et al*., 1993. Cardiac effects of longterm thryotropin suppressive therapy with levothyroxine. J. Clin. Endocrinol. Metab., 77: 334-338.

Biondi, B., S. Fazio, A. Cuocolo, D. Sabatini and E. Nicolai *et al*., 1996. Impaired cardiac reserve and exercise capacity in patients receiving long term thyrotropin suppressive therapy with levothyroxine. J. Clin. Endocrinol. Metab., 81: 4224-4228.

Brabant, G., P. Beck-Peccoz, B. Jarzab, P. Laurberg and J. Orgiazzi *et al*., 2006. Is there a need to redefine the upper normal limit of TSH? Eur. J. Endocrinol., 154: 633-637.

Burman, K.D., 2009. Controversies surrounding pregnancy, maternal thyroid status and fetal outcome. Thyroid, 19: 323-326.

Canaris, G.J., N.R. Manowitz, G. Mayor and E.C. Ridgway, 2000. The colorado thyroid disease prevalence study. Arch. Int. Med., 160: 526-534.

Cappola, A.R., L.P. Fried, A.M. Arnold, M.D. Danese and L.H. Kuller *et al*., 2006. Thyroid status, cardiovascular risk and mortality in older adults. J. Am. Med. Assoc., 295: 1033-1041.

Casey, B.M., J.S. Dashe, C.E. Wells, D.D. McIntire, W. Byrd, K.J. Leveno and F.G. Cunningham, 2005. Subclinical hypothyroidism and pregnancy outcomes. Obstetrics Gynecol., 105: 239-245.

Casey, B.M., J.S. Dashe, C.E. Wells, D.D. McIntire, K.J. Leveno and F.G. Cunningham, 2006. Subclinical hyperthyroidism and pregnancy outcomes. Obstetrics Gynecol., 107: 337-341.

Chadarevian, R., E. Bruckert, L. Leenhardt, P. Giral, A. Ankri and G. Turpin, 2001. Components of the fibrinolytic system are differently altered in moderate and severe hypothyroidism. J. Clin. Endocrinol. Metab., 86: 732-737.

Chaler, E.A., R. Fiorenzano, C. Chilelli, V. Llinares and G. Areny *et al*., 2012. Age-specific thyroid hormone and thyrotropin reference intervals for a pediatric and adolescent population. Clin. Chem. Lab. Med., 50: 885-890.

Chu, J.W., P.N. Kao, J.L. Faul and R.L. Doyle, 2002. High prevalence of autoimmune thyroid disease in pulmonary arterial hypertension. Chest, 122: 1668-1673.

Colao, A., R. Pivonello, A. Faggiano, M. Filippella and D. Ferone *et al*., 2000. Increased prevalence of thyroid autoimmunity in patients successfully treated for Cushing's disease. Clin. Endocrinol., 53: 13-19.

Coles, A.J., M. Wing, S. Smith, F. Coraddu and S. Greer *et al*., 1999. Pulsed monoclonal antibody treatment and autoimmune thyroid disease in multiple sclerosis. Lancet, 354: 1691-1695.

Cooper, D.S., 2004. Subclinical thyroid disease: Consensus or conundrum? Clin. Endocrinol., 60: 410-412.

Covinsky, M., O. Laterza, J.D. Pfeifer, T. Farkas-Szallasi and M.G. Scott, 2000. An IgM ë antibody to *Escherichia coli* produces false-positive results in multiple immunometric assays. Clin. Chem., 46: 1157-1161.

D'Herbomez, M., G. Forzy, F. Gasser, C. Massart, A. Beaudonnet and R. Sapin, 2003. Clinical evaluation of nine free thyroxine assays: Persistent problems in particular populations. Clin. Chem. Lab. Med., 41: 942-947.

Danese, M.D., N.R. Powe, C.T. Sawin and P.W. Ladenson-Jama, 1996. Screening for mild thyroid failure at the periodic examination: A decision and cost-effectiveness analysis. Am. Med. Assoc., 276: 285-292.

Danese, M.D., P.W. Landenson, C.L. Meinert and N.R Powe, 2000. Clinical review 115: Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: A quantitative review of the literature. J. Clin. Endocrinal. Metab., 85: 2993-3001.

Delange, F., 1997. Neonatal screening for congenital hypothyroidism: Results and perspectives. Hormone Res., 48: 51-61.

Effraimidis, G., T.G. Strieder, J.G. Tijssen and W.M. Wiersinga, 2011. Natural history of the transition from euthyroidism to overt autoimmune hypo-or hyperthyroidism: A prospective study. Eur. J. Endocrinol., 164: 107-113.

Eggertsen, R., K. Petersen, P.A. Lundberg, E. Nystrom and G. Lindstedt, 1988. Screening for thyroid disease in a primary care unit with a thyroid stimulating hormone assay with a low detection limit. Br. Med. J., 297: 1586-1592.

Ercan-Fang, S., H.L. Schwartz, C.N. Mariash and J.H. Oppenheimer, 2000. Quantitative assessment of pituitary resistance to thyroid hormone from plots of the logarithm of thyrotropin versus serum free thyroxine index. J. Clin. Endocrinol. Metab., 85: 2299-2303.

Erickson, A.R., R.J. Enzenauer, D.M. Nordstrom and J.A. Merenich, 1994. The prevalence of hypothyroidism in gout. Am. J. Med., 97: 231-234.

Eskes, S.A. and W.M. Wiersinga, 2009. Amiodarone and thyroid. Best Pract. Res. Clin. Endocrinol. Metab., 23: 735-751.

Fade, J.V., J.A. Franklyn, K.W. Cross, S.C. Jones and M.C. Sheppard, 1991. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin. Endocrinol., 34: 77-84.

Fillee, C., J. Cumps and J.M. Ketelslegers, 2012. Comparison of three free T4 (FT4) and free T3 (FT3) immunoassays in healthy subjects and patients with thyroid diseases and severe non-thyroidal illnesses. Clin. Lab., 58: 725-736.

Fisher, D.L., 1997. The hypothyroxinemia of prematurity. J. Clin. Endocrinol. Metab., 82: 1701-1703.

Flynn, R.W., S.R. Bonellie, R.T. Jung, T.M. MacDonald and A.D. Morris *et al*., 2010. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. J. Clin. Endocrinol. Metab., 95: 186-193.

Ghori, F., K.D. Polder, L.C. Pinter-Brown, A.O. Hoff, R.F. Gagel, S.I. Sherman and M. Duvic, 2006. Thyrotoxicosis after denileukin diftitox therapy in patients with mycosis fungoides. J. Clin. Endocrinol. Metab., 91: 2205-2208.

Giustarini, E., A. Pinchera, P. Fierabracci, M. Roncella, L. Fustaino, C. Mammoli and C. Giani, 2006. Thyroid autoimmunity in patients with malignant and benign breast diseases before surgery. Eur. J. Endocrinol., 154: 645-649.

Goday-Arno, A., M. Cerda-Esteva, J.A. Flores-Le-Roux, J.J. Chillaron-Jordan, J.M. Corretger and J.F. Cano-Perez, 2009. Hyperthyroidism in a population with Down syndrome (DS). Clin. Endocrinol., 71: 110-114.

Haggerty Jr., J.J., R.A. Stern, G.A. Mason, J. Beckwith, C.E. Morey and A.J. Prange Jr., 1993. Subclinical hypothyroidism: A modifiable risk factor for depression? Am. J. Psychiatry, 150: 508-510.

Hak, A.E., H.A.P. Pols, T.J. Visser, H.A. Drexhage, A. Hofman and J.C.M. Witteman, 2000. Subclinical hypothyroidism is an independent risk factor for arthreosclerosis and myocardial infarction in elderly women: The rotterdam study. Ann. Intern. Med., 132: 270-278.

Hallengren, B., M. Lantz, B. Andreasson and L. Grennert, 2009. Pregnant women on thyroid substitution are often dysregulated in early pregnancy. Thyroid, 19: 391-394.

Hamilton, T.E., S. Davis, L. Onstad and K.J. Kopecky, 2008. Thyrotropin levels in a population with no clinical, autoantibody, or ultrasonographic evidence of thyroid disease: Implications for the diagnosis of subclinical hypothyroidism. J. Clin. Endocrinol. Metab., 93: 1224-1230.

Helfand, M. and C.C. Redfern, 1998. Screening for thyroid disease: An update. Ann. Intern. Med., 129: 144-158.

Hershman, J.M., A.E. Pekary, L. Berg, D.H. Solomon and C.T. Sawin, 1993. Serum thyrotropin and thyroid hormone levels in elderly and middle-aged euthyroid persons. J. Am. Geriatr. Soc., 41: 823-828.

Hollowell, J.G., N.W. Staehling, W.D. Flanders, W.H. Hannon, E.W. Gunter, C.A. Spencer and L.E. Braverman, 2002. Serum TSH, T4 and thyroid antibodies in the United States population (1988 to 1994): National health and nutrition examination survey (NHANES III). J. Clin. Endocrinol. Metab., 87: 489-499.

Horacek, J., S. Spitalnikova, B. Dlabalova, E. Malirova and J. Vizda *et al*., 2010. Universal screening detects two-times more thyroid disorders in early pregnancy than targeted high-risk case finding. Eur. J. Endocrinol., 163: 645-650.

Huber, G., J.J. Staub, C. Meier, C. Mitrache, M. Guglielmetti, P. Huber and L.E. Braverman, 2002. Prospective study of the spontaneous course of subclinical hypothyroidism: Prognostic value of thyrotropin, thyroid reserve and thyroid antibodies. J. Clin. Endocrinol. Metab., 87: 3221-3226.

Ismail, A.A.A., P.L. Walker, M.L. Cawood and J.H. Barth, 2002. Interference in immunoassay is an underestimated problem. Ann. Clin. Biochem., 39: 366-373.

Janssen, O.E., N. Mehlmauer, S. Hahn, A.H. Offner and R. Gartner, 2004. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Eur. J. Endocrinol., 150: 363-369.

Jarlov, A.E., B. Nygaard, L. Hegedus, S.G. Hartling and J.M. Hansen, 1998. Observer variation in the clinical and laboratory evaluation of patients with thyroid dysfunction and goiter. Thyroid, 8: 393-398.

Jenkins, R.C. and A.P. Weetman, 2002. Disease associations with autoimmune thyroid disease. Thyroid, 12: 977-988.

Jorde, R., K. Waterloo, H. Storhaug, A. Nyrnes, J. Sundsfjord and T.G. Jenssen, 2006. Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. J. Clin. Endocrinol. Metab., 91: 145-153.

Kahaly, G.J., 2000. Cardiovascular and atherogenic aspects of subclinical hypothyroidism. Thyroid, 10: 665-679.

Kailajarvi, M., T. Takala, P. Gronroos, N. Tryding, J. Viikari, K. Irjala and J. Forsstrom, 2000. Reminders of drug effects on laboratory test results. Clin. Chem., 46: 1395-1400.

Kaptein, E.M., 1996. Thyroid hormone metabolism and thyroid diseases in chronic renal failure. Endocr. Rev., 17: 45-63.

Klein, I. and K. Ojamaa, 2001. Thyroid hormones and the heart. N. Engl. J. Med., 344: 501-509.

Kricka, L.J., 2000. Interferences in immunoassay-still a threat. Clin. Chem., 46: 1037-1038.

Kung, A.W. and E.D. Janus, 1996. Thyroid dysfunction in ambulatory elderly Chinese subjects in an area of borderline iodine intake. Thyroid, 6: 111-114.

LaFranchi, S., 1999. Congenital hypothyroidism: Etiologies, diagnosis and management. Thyroid, 9: 735-740.

Lazarus, J., 2011. The continuing saga of postpartum thyroiditis. J. Clin. Endocrinol. Metab., 96: 614-616.

Lazarus, J.H., 2007. Aspects of treatment of subclinical thyroid dysfunction. Thyroid, 17: 313-316.

Lebeau, S. and S.J. Mandel, 2006. Thyroid disorders during pregnancy. Endocrinol. Metab. Clin. N. Am., 35: 117-136.

Lee, R.H., C.A. Spencer, J.H. Mestman, E.A. Miller, I. Petrovic, L.E. Braverman and T.M. Goodwin, 2009. Free T4 assays are flawed during pregnancy. Am. J. Obstet Gynecol., 200: 260-260.

Lekakis, J., C. Papamichael, M. Alevizaki, G. Piperingos and P. Marafelia *et al*., 1997. Flow-mediated, endothelium-dependent vasodilation is impaired in subjects with hypothyroidism, borderline hypothyroidism and high-normal serum thyrotropin (TSH) values. Thyroid, 7: 411-414.

Luton, D., I. Le Gac, E. Vuillard, M. Castanet and J. Guibourdenche *et al*., 2005. Management of Graves disease during pregnancy: The key role of fetal thyroid gland monitoring. J. Clin. Endocrinol. Metab., 90: 6093-6098.

Mansourian, A.R., E.O. Ghaemi, A.R. Ahmadi, A. Saifi, A.V. Moradi and S. Bakhshandeh-Nosrat, 2007. A survey of urinary iodine concentration in South-East of Caspian Sea in Northern, Iran. Pak. J. Biol. Sci., 10: 2166-2171.

Mansourian, A.R., E. Ghaemi, A.R. Ahmadi, A. Marjani, A. Saifi and S. Bakhshandehnosrat, 2008. Serum lipid level alterations in subclinical hypothyroid patients in Gorgan (South East of Caspian Sea). Chinese Clin. Med., 3: 206-210.

Mansourian, A.R., 2010a. A review on hyperthyroidism: Thyrotoxicosis under surveillance. Pak. J. Biol. Sci., 13: 1066-1076.

Mansourian, A.R., 2010b. A review on post-puberty Hypothyroidism: A glance at myxedema. Pak. J. Biol. Sci., 13: 866-876.

Mansourian, A.R., 2010c. The immune system which adversely alter thyroid functions: A review on the concept of autoimmunity. Pak. J. Biol. Sci., 13: 765-774.

Mansourian, A.R., 2010d. The state of serum lipids profiles in sub-clinical hypothyroidism: A review of the literature. Pak. J. Biol. Sci., 13: 556-562.

Mansourian, A.R., 2010e. Thyroid function tests during first-trimester of pregnancy: A review of literature. Pak. J. Biol. Sci., 13: 664-673.

Mansourian, A.R. and A.R. Ahmadi, 2010f. Correlation between inverse age and serum thyroxine level among children and adolescents. J. Clin. Diagn. Res., 4: 3196-3200.

Mansourian, A.R., A.R. Ahmadi, A. Saifi and S. Bakhshandehnosrat, 2010g. The children reference range of thyroid hormones in Northern Iran. Pak. J. Biol. Sci., 13: 862-865.

Mansourian, A.R., A.R. Ahmadi, H.R. Mansourian, A. Saifi, A. Marjani, G.R. Veghari and E. Ghaemi, 2010h. Maternal thyroid stimulating hormone level during the first trimester of pregnancy at the South-East of the caspian sea in Iran. J. Clin. Diagn. Res., 4: 2472-2477.

Mansourian, A.R., 2011a. A review on the metabolic disorders of iodine deficiency. Pak. J. Biol. Sci., 14: 412-424.

Mansourian, A.R., 2011b. Abnormal serum thyroid hormones concentration with healthy functional gland: A review on the metabolic role of thyroid hormones transporter proteins. Pak. J. Biol. Sci., 14: 313-326.

Mansourian, A.R., 2011c. Central dogma in thyroid dysfunction: A review on structure modification of TSHR as a cornerstone for thyroid abnormalities. Pak. J. Biol. Sci., 14: 170-181.

Mansourian, A.R., 2011d. Metabolic pathways of tetraidothyronine and triidothyronine production by thyroid gland: A review of articles. Pak. J. Biol. Sci., 14: 1-12.

Mansourian, A.R., A. Sifi and H.R. Mansourian, 2011e. Serum thyroxin level during the first-trimester of pregnancy. J. Clin. Diagn. Res., 5: 733-736.

Mansourian, A.R., G.R. Asaifi and G.R. Veghari, 2011f. The prevalence of elevation of serum alanine amino transferase at Gorgan in northern Iran. J. Clin. Diagn. Res., 15: 246-248.

Mansourian, A.R., 2012a. A literature review on the adverse effect of hypothyroism on kidney function. Pak. J. Biol. Sci., 15: 709-719.

Mansourian, A.R., 2012b. A review of literature on the adverse effects of hyperthyroidism on the heart functional behavior. Pak. J. Biol. Sci., 15: 164-176.

Mansourian, A.R., 2012c. A review on cardiovascular diseases originated from subclinical hypothyroidism. Pak. J. Biol. Sci., 15: 58-67.

Martin, F.I., B.W. Tress, P.G. Colman and D.R. Deam, 1993. Iodine-induced hyperthyroidism due to nonionic contrast radiography in the eldery. Am. J. Med., 95: 78-82.

McDermott, M.T. and E.C. Ridgway, 2001. Subclinical hypothyroidism is mild thyroid failure and should be treated. J. Clin. Endocrinol. Metab., 86: 4585-4590.

Mebis, L., Y. Debaveye, T.J. Visser and G. Van den Berghe, 2006. Changes within the thyroid axis during the course of critical illness. Endocrinol. Metab. Clin. N. Am., 35: 807-821.

Meier, C., J.J. Staub, C.B. Roth, M. Guglielmetti and M. Kunz *et al*., 2001. TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: A double blind, placebo-controlled trial (Basel Thyroid Study). J. Clin. Endocrinol. Metab., 86: 4860-4866.

Meyerovitch, J., P. Rotman-Pikielny, M. Sherf, E. Battat, Y. Levy and M.I. Surks, 2007. Serum thyrotropin measurements in the community: Five-year follow-up in a large network of primary care physicians. Arch. Int. Med., 167: 1533-1538.

Monzani, F., P. del Guerra, N. Caraccio, C.A. Pruneti, E. Pucci, M. Luisi and L. Baschieri, 1993. Subclinical hypothyroidism: Neurobehavioral features and beneficial effect of L-thyroxine treatment. Clin. Invest., 71: 367-371.

Monzani, F., V. Di Bello, N. Caraccio, A. Bertini, D. Giorgi, C. Giusti and E. Ferrannini, 2001. Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: A double blind, placebo-controlled study. J. Clin. Endocrinol. Metabolism, 86: 1110-1115.

Morley, J.E., 1981. Neuroendocrine control of thyrotropin secretion. Endocr. Rev., 2: 396-436.

Nagasaki, T., M. Inaba, S. Yamada, K. Shirakawa and Y. Nagata *et al*., 2009. Decrease of brachial-ankle pulse wave velocity in female subclinical hypothyroid patients during normalization of thyroid function: A double-blind, placebo-controlled study. Eur. J. Endocrinol., 160: 409-415.

Negro, R., G. Formoso, T. Mangieri, A. Pezzarossa, D. Dazzi and H. Hassan, 2006. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: Effects on obstetrical complications. J. Clin. Endocrinol. Metab., 91: 2587-2591.

Nicoloff, J.T. and C.A. Spencer, 1990. The use and misuse of the sensitive thyrotropin assays. J. Clin. Endocrinol. Metab., 71: 553-558.

Niepomniszczse, H., F. Pitoia, S.B. Katz, R. Chervin and O.D. Bruno, 2002. Primary thyroid disorders in endogenous Cushing's syndrome. Eur. J. Endocrinol., 147: 305-311.

Nystrom, E., K. Caidahl, G. Fager, C. Wikkelso, P.A. Lundberg and G. Lindstedt, 1988. A double-bind cross-over 12-month study of L-thyroxine treatment of women with subclinical hypothroidism. Clin. Endocrinol., 29: 63-75.

Owen, P.J., C. Rajiv, D. Vinereanu, T. Mathew, A.G. Fraser and J.H. Lazarus, 2006. Subclinical hypothyroidism, arterial stiffnss and myocardial reserve. J. Clin. Endocrinol. Metab., 91: 2126-2132.

Parle, J.V., P. Maissoneuve P, M.C. Sheppard, P. Boyle and J.A. Franklyn, 2001. Prediction of all cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: A 10 year cohort study. Lancet, 358: 861-865.

Paulides, M., H.G. Dorr, W. Stohr, S. Bielack and E. Koscielniak *et al*., 2007. Thyroid function in paediatric and young adult patients after sarcoma therapy: A report from the Late Effects Surveillance System. Clin. Endocrinol., 66: 727-731.

Peterson, K., G. Lindstedt, P.A. Lundberg, C. Bengtsson, L. Lapidus and E. Nystrom, 1991. Thyroid disease in middle-aged and elderly Swedish women: Thyroid related hormones, thyroid dysfunction and goiter in relation to age and smoking. J. Internal Med., 229: 407-413.

Petta, C.A., M.S. Arruda, D.E. Zantut-Wittmann and C.L. Benetti-Pinto, 2007. Thyroid autoimmunity and thyroid dysfunction in women with endometriosis. Hum. Reprod., 22: 2693-2697.

Poretti, S., C. Giavoli, C. Ronchi, G. Lombardi and M. Zaccaria *et al*., 2002. Recombinant human GH replacement therapy and thyroid function in a large group of adult GH-deficient patients: When does L-T4 therapy become mandatory? J. Clin. Endocrinol. Metab., 87: 2042-2045.

Ransohoff, D.F. and A.R. Feinstein, 1978. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. N. Engl. J. Med., 299: 926-930.

Razvi, S., J.U. Weaver, M.P. Vanderpump and S.H. Pearce, 2010. The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: Reanalysis of the Wickham survey cohort. J. Clin. Endocrinol. Metab., 95: 1734-1740.

Rodondi, N., A.B. Newman, E. Vittinghoff, N. de Rekeneire, S. Satterfield, T.B. Harris and D.C. Bauer, 2005. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events and death. Arch. Int. Med., 165: 2460-2466.

Rodondi, N., D. Aujesky, E. Vittinghoff, J. Cornuz and D.C. Bauer, 2006. Subclinical hypothyroidism and the risk of coronary heart disease: A meta-analysis. Am. J. Med., 119: 541-551.

Rooman RP, M.V. Du Caju, L.O. De Beeck, M. Docx, P. Van Reempts and K.J. Van Acker, 1996. Low thyroxinemia occurs in the majority of very preterm newborns. Eur. J. Pediatr., 155: 211-215.

Ross, D.S., 1994. Hyperthyroidism, thyroid hormone therapy and bone. Thyroid, 4: 319-326.

Roti, E., E. Gardini, R. Minelli, L. Bianconi and M. Flisi, 1991. Thyroid function evaluation by different commercially available free thyroid hormone measurement kits in term pregnant women and their newborns. J. Endocrinol. Invest., 14: 1-9.

Sapin, R. and M. d'Herbomez, 2003. Free thyroxine measured by equilibrium dialysis and nine immunoassays in sera with various serum thyroxine-binding capacities. Clin. Chem., 49: 1531-1535.

Sato, T., Y. Suzuki, T. Taketani, K. Ishiguro and H. Nakajima, 1977. Age-related change in pituitary threshold for TSH release during thyroxine replacement therapy for cretinism. J. Clin. Endocrinol. Metab., 44: 553-559.

Sawin, C.T., A. Geller, P.A. Wolf, A.J. Belanger and E. Baker *et al*., 1994. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N. Engl. J. Med., 331: 1249-1252.

Schectman, J.M., E.G. Elinsky and L.G. Pawlson, 1991. Effect of education and feedback on thyroid function testing strategies of primary care clinicians. Arch. Intern. Med., 151: 2163-2166.

Schmiegelow, M., U. Feldt-Rasmussen, A.K. Rasmussen, H.S. Poulsen and J. Muller, 2003. A population-based study of thyroid function after radiotherapy and chemotherapy for a childhood brain tumor. J. Clin. Endocrinol. Metab., 88: 136-140.

Shahmohammdi, F., A.R. Mansourian and H.R. Mansourian, 2008. Serum thyroid hormone level in women with nausea and vomiting in early pregnancy. J. Med. Sci., 8: 507-510.

Sinard, R.J., E.J. Tobin, E.L. Mazzaferri, S.E. Hodgson and D.C. Young *et al*., 2000. Hypothyroidism after treatment for nonthyroid head and neck cancer. Arch. Otolaryngol., 126: 652-657.

Sklar, C., J. Whitton, A. Mertens, M. Stovall and D. Green *et al*., 2000. Abnormalities of the thyroid in survivors of Hodgkin's disease: Data from a childhood cancer survivor study. J. Clin. Endocrinol. Metab., 85: 3227-3232.

Stagnaro-Green, A., A. Schwartz, R. Gismondi, A. Tinelli, T. Mangieri and R. Negro, 2011. High rate of persistent hypothyroidism in a large-scale prospective study of postpartum thyroiditis in southern Italy. J. Clin. Endocrinol. Metab., 96: 652-657.

Stott, D.J., A.R. McLellan, J. Findlayson, P. Chu and W.D. Alexander, 1991. Elderly patients with suppressed serum TSH but normal free thyroid hormone levels usually have mild thyroid overactivity and are at increased risk of developing overt hyperthyroidism. Q. J. Med., 78: 77-84.

Stricker, Rt., M. Echenard, R. Eberhart, M.C. Chevailler, V. Perez, F.A. Quinn and R. Stricker, 2007. Evaluation of maternal thyroid function during pregnancy: The importance of using gestational age-specific reference intervals. Eur. J. Endocrinol., 157: 509-514.

Stuckey, B.G.A., G.N. Kent and J.R. Allen, 2001. The biochemical and clinical course of postpartum thyroid dysfunction: The treatment decision. Clin. Endocrinol., 54: 377-383.

Stuckey, B.G.A., D. Yeap and S.R. Turner, 2010. Thyroxine replacement during super-ovulation for *in vitro* fertilization: A potential gap in management? Fert. Ster., 93: 2414.e1-2414.e3.

Surks, M.I., E. Ortiz, G.H. Daniels, C.T. Sawin and N.F. Col *et al*., 2004. Subclinical thyroid disease: Scientific review and guidelines for diagnosis and management. JAMA., 291: 228-238.

Surks, M.I., 2005. Subclinical thyroid dysfunction. J. Clin. Endocrinol. Metab., 90: 586-587.

Surks, M.I., G. Goswami and G.H. Daniels, 2005. The thyrotropin reference range should remain unchanged. J. Clin. Endocrinol. Metab., 90: 5489-5496.

Surks, M.I. and L. Boucai, 2010. Age-and race-based serum throtropin reference limits. J. Clin. Endocrinol. Metab., 95: 496-502.

Szabolcs, I., J. Podoba, J. Feldkamp, O. Dohan and I. Farkas *et al*., 1997. Comparative screening for thyroid disorders in old age in areas of iodine deficiency, long-term iodine prophylaxis and abundant iodine intake. Clin. Endocrinol., 47: 87-92.

Thangaratinam, S., A. Tan, E. Knox, M.D. Kilby, J. Franklyn and A. Coomarasamy, 2011. Association between thyroid autoantibodies and miscarriage and preterm birth: Meta-analysis of evidence. Br. Med. J., Vol. 342. 10.1136/bmj.d2616

Thompson, G.R., A.K. Soutar, F.A. Spengel, A. Jadhav, S.J. Gavigan and N.B. Myant, 1981. Defects of receptor-mediated low density lipoprotein catabolism in homozygous familial hypercholesterolemia and hypothyroidism *in vivo*. Proc. Nat. Acad. Sci. USA., 78: 2591-2595.

Thung, S.F., E.F. Funai and W.A. Grobman, 2009. The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism. Am. J. Obstet. Gynecol., 267: e1-e7.

Toubert, M.E., S. Chevret, B. Cassinat, M.H. Schlageter, J.P. Beressi and J.D. Rain, 2000. From guidelines to hospital practice: Reducing inappropriate ordering of thyroid hormone and antibody tests. Eur. J. Endocrinol., 142: 605-610.

Tunbridge, W.M., D.C. Evered, R. Hall, D. Appleton and M. Brewis *et al*., 1977. The spectrum of thyroid disease in a community: The Whickham survey. Clin. Endocrinol., 7: 481-493.

Vaidya, B., S. Anthony, M. Bilous, B. Shields, J. Drury, S. Hutchison and R. Bilous, 2007. Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? J. Clin. Endocrinol. Metab., 92: 203-207.

Van den Berghe, G., P. Wouters, F. Weekers, S. Mohan and R.C. Baxter *et al*., 1999. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptides and thyrotropin-releasing hormone in patients with protracted critical illness. J. Clin. Endocrinol. Metab., 84: 1311-1323.

Vanderpump, M.P.J., W.M.G. Tunbridge, J.M. French, D. Appleton and D. Bates *et al*., 1995. The incidence of thyroid disorders in the community: A twenty-year follow-up of the Whickham survey. Clin. Endocrinol., 43: 55-68.

Volzke, H., C. Schwahn, H. Wallaschofski and M. Dorr, 2007. Review: The association of thyroid dysfunction with all-caus and circulatory mortality: Is there a causal relatinship?. J. Clin. Endocrinol. Meta, 92: 2421-2429.

Wartofsky, L. and D.J. Handelsman, 2010. Standardization of hormonal assays for the 21st century. J. Clin. Endocrinol. Metab., 95: 5141-5143.

Wartofsky, L. and R.A. Dickey, 2005. The evidence for a narrower thyrotropin reference range is compelling. J. Clin. Endocrinol. Metab., 90: 5483-5488.

Waterhouse, D.F., A.M. McLaughlin, C.D. Walsh, F. Sheehan and D. O'Shea, 2007. An examination of the relationship between normal range thyrotropin and cardiovascular risk parameters: A study in healthy women. Thyroid, 17: 243-248.

Weetman, A.P., 1997. Hypothyroidism: Screening and subclinical disease. Br. Med. J., 314: 1175-1178.

Wesche, M.F.T., M.M.C. T.V Buul, P. Lips, N.J. Smits and W.M. Wiersinga, 2001. A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goitre. J. Clin. Endocrinol. Metab., 86: 998-1005.

Wiebolt, J., R. Achterbergh, A. den Boer, S. van der Leij and E. Marsch *et al*., 2011. Clustering of additional autoimmunity behaves differently in Hashimoto patients compared with Graves patients. Eur. J. Endocrinol., 164: 789-794.

Woeber, K.A., 2005. Observations concerning the natural history of subclinical hyperthyroidism. Thyroid, 15: 687-691.

Zervas, A., A. Katopodi, A. Protonotariou, S. Livadas, M. Karagiorga, C. Politis and G. Tolis, 2002. Assessment of thyroid function in two hundred patients with β-thalassemia major. Thyroid, 12: 151-154.

Zhu, L., X. Zhang, X. He, X. Yang, Y. Wang, C. Wang and Z. Feng, 2013. Reference intervals for serum thyroid hormones in preterm hospitalized infants. J. Pediatr. Endocrinol. Metab., 15: 1-5..

Zulewski, H., B. Muller, P. Exer, A.R. Miserez and J.J. Staub, 1997. Estimation of tissue hypothyroidism by a new clinical score: Evaluation of patients with various grades of hypothyroidism and controls. J. Clin. Endocrinol. Metab., 82: 771-776.